

Saquinavir

Brand Name: Fortovase, Invirase

Drug Class: Protease Inhibitors



Drug Description

Saquinavir is a peptidomimetic protease inhibitor (PI). [1]

HIV/AIDS-Related Uses

Saquinavir mesylate was approved by the FDA on December 6, 1995. Saquinavir was approved by the FDA on November 7, 1997. Both are indicated for use in combination with other antiretroviral agents for the treatment of HIV infection. Saquinavir soft gelatin capsules and saquinavir mesylate tablets and hard gelatin capsules are not bioequivalent. Saquinavir mesylate, marketed as Invirase, must be combined with zidovudine to provide plasma saquinavir levels at least equal to those achieved with saquinavir, marketed as Fortovase.[2] [3] [4]

Because of a decline in clinical demand for Fortovase, this formulation will be discontinued by the manufacturer by February 15, 2006. Saquinavir mesylate, now the preferred formulation, will continue to be available. Saquinavir mesylate offers distinct advantages over the saquinavir soft gelatin formulation, including a lower pill burden, smaller pill size, easier storage requirements, and improved gastrointestinal tolerance.[5]

Pharmacology

Saquinavir is a structural analogue of the HIV Phe-Pro protease cleavage site and is a selective, competitive, reversible inhibitor of HIV-1 and HIV-2 protease. Saquinavir is active in both acutely and chronically infected cells; chronically infected cells are not affected by nucleoside reverse transcriptase inhibitors (NRTIs). While saquinavir does not affect early stages of the HIV replication cycle, it does interfere with the production of infectious virions, limiting further infectious spread of the virus.[6]

Bioavailability of saquinavir mesylate from hard gelatin capsules is low, averaging 4%. The relative bioavailability of saquinavir in liquid-filled soft gelatin capsules is estimated to average 331% that of saquinavir mesylate hard gelatin capsules. This represents a calculated average oral bioavailability

from the soft gelatin capsules of 13%. Peak plasma concentrations and area under the concentration-time curve (AUC) of the drug in soft gelatin capsules are about two times higher in HIV-infected patients than in healthy volunteers.[7]

Distribution of the drug into body tissues and fluids (such as cerebrospinal fluid) has not been fully characterized. Saquinavir is about 97% bound to plasma proteins in concentrations up to 30 mcg/ml. The drug is metabolized in the liver to several monohydroxylated and dihydroxylated inactive metabolites. Metabolism is mediated by cytochrome P450; the isoenzyme CYP3A4 is involved in more than 90% of this metabolism. Systemic clearance is rapid. Saquinavir is excreted primarily in the feces, both as unchanged drug and as metabolites.[8]

Saquinavir is in FDA Pregnancy Category B. It is not known whether saquinavir crosses the placenta in humans; placental transfer in laboratory animals is less than 5% of maternal plasma concentrations.[9] There are no adequate and well-controlled studies in pregnant women. Saquinavir should be used during pregnancy only when clearly needed. An Antiretroviral Pregnancy Registry has been established to monitor the outcomes of pregnant women exposed to antiretroviral agents, including saquinavir. Physicians are encouraged to register patients by calling 1-800-258-4263 or online at <http://www.APRegistry.com>. [10] It is not known whether saquinavir is secreted in human milk; however, it is secreted in the milk of laboratory rats.[11]

Because saquinavir is metabolized by the liver, the manufacturer recommends that it be used with caution in patients with hepatic insufficiency. Patients with baseline liver function test results higher than five times the upper limit of normal were not included in clinical studies.[12]

HIV isolates with reduced susceptibility to the drug have been recovered from some patients on long-term saquinavir therapy. Genotypic analysis showed that mutations at amino acid positions 48 and/or 90 of the HIV protease gene were

Saquinavir

Pharmacology (cont.)

consistently associated with saquinavir resistance, and mutations at these positions have not been detected in isolates from PI-naïve patients.[13]

Cross resistance among PIs has been recognized; saquinavir-resistant isolates from patients on long-term therapy showed resistance to at least one of the following four PIs: indinavir, nelfinavir, ritonavir, and amprenavir.[14] Cross resistance between saquinavir and NRTIs or non-nucleoside reverse transcriptase inhibitors (NNRTIs) is unlikely because these drugs have different target enzymes.[15] In vitro studies indicate that the antiretroviral effects of PIs and some NRTIs or NNRTIs may be additive or synergistic.[16]

Adverse Events/Toxicity

Saquinavir and saquinavir mesylate appear to be well tolerated. In clinical studies, the most frequently reported adverse effects included abdominal discomfort, diarrhea, and nausea. Other reactions include abdominal pain, anxiety, asthenia, buccal mucosa ulceration, constipation, depression, dizziness, dyspepsia, eczema, fatigue, flatulence, headache, insomnia, libido disorder, musculoskeletal pain, numbness in extremities, paresthesia, peripheral neuropathy, rash, taste perversion, verruca, and vomiting.[17] [18]

Body fat accumulation and redistribution, increased bleeding in hemophilia patients, hyperglycemia, exacerbation of existing diabetes mellitus, and new onset diabetes mellitus have been reported in patients receiving PIs, including saquinavir.[19]

In clinical studies there have been rare reports of serious adverse effects that may be related to treatment with saquinavir or saquinavir mesylate. These rare effects included confusion, ataxia, and weakness; seizures; headache; acute myeloblastic leukemia; hemolytic anemia; thrombocytopenia; thrombocytopenia and intracranial hemorrhage resulting in death; attempted suicide; Stevens-Johnson syndrome; bullous skin eruptions and polyarthritis; severe cutaneous reaction associated with increased liver function test results; isolated elevation of transaminase values; exacerbation of chronic liver disease with elevated

liver function tests, jaundice, ascites, and upper left and right quadrant abdominal pain; fatal pancreatitis; intestinal obstruction; portal hypertension; thrombophlebitis; peripheral vasoconstriction; drug fever; nephrolithiasis; and acute renal insufficiency.[20]

Drug and Food Interactions

Presence of food in the gastrointestinal tract can substantially increase the absorption of saquinavir and saquinavir mesylate. Administering saquinavir mesylate hard gelatin capsules with a meal increases absorption five- to tenfold compared with administration on an empty stomach.[21] For saquinavir liquid-filled soft gelatin capsules, the mean 12-hour AUC increased from 167 ng h/ml under fasting conditions to 1120 ng h/ml when administered with food.[22] Limited data indicate that the bioavailability of saquinavir is increased when the drug is administered with grapefruit juice.[23]

Concomitant use of certain other antiretroviral agents with saquinavir or saquinavir mesylate may significantly increase or decrease saquinavir plasma concentrations.[24] [25] Efavirenz taken with saquinavir results in decreased concentrations of both drugs.[26] The coformulation of lopinavir/ritonavir taken with saquinavir decreases the serum concentration of ritonavir.[27] Delavirdine, indinavir, or nelfinavir taken with saquinavir increases the serum concentration of saquinavir.[28]

Ritonavir taken with saquinavir increases the serum concentration of saquinavir.[29] There have been other studies of the effects of certain antiretrovirals when used with saquinavir boosted with ritonavir. Atazanavir taken with saquinavir boosted with ritonavir increases the serum concentrations of both saquinavir and ritonavir.[30] Fosamprenavir taken with saquinavir boosted with ritonavir decreases the serum concentration of saquinavir.[31]

Metabolism of saquinavir is mediated by the cytochrome P (CYP) 450 isoenzyme CYP3A4. Drugs that induce this isoenzyme may reduce saquinavir plasma concentrations. Conversely, drugs that inhibit this isoenzyme may increase plasma concentrations of saquinavir. Saquinavir

Saquinavir



Drug and Food Interactions (cont.)

may alter the pharmacokinetics of other drugs that are metabolized by this enzyme system, which may create the possibility of serious adverse effects.[32]

Use of saquinavir or saquinavir mesylate with lovastatin or simvastatin is not recommended. Caution should be used when any PIs, including saquinavir, are used concurrently with other HMG-CoA reductase inhibitors that are metabolized by the CYP3A4 pathway (e.g., atorvastatin or cerivastatin). The resulting increased concentration of statins may increase the risk of myopathy or rhabdomyolysis.[33] [34]

Use of saquinavir or saquinavir mesylate with St. John's wort (*Hypericum perforatum*) or products containing St. John's wort may substantially decrease saquinavir concentrations and may lead to loss of virologic response and possible resistance to saquinavir or other protease inhibitors.[35] [36]

Saquinavir should not be coadministered with astemizole, cisapride, or terfenadine (no longer available in the United States). Other drugs, including midazolam, triazolam, and ergot derivatives should not be coadministered with saquinavir. Competition for CYP3A4 by saquinavir may inhibit the metabolism of these drugs, which could potentially cause serious or life-threatening reactions, such as cardiac arrhythmias or prolonged sedation.[37] [38]

Coadministration of certain other drugs with saquinavir or saquinavir mesylate may cause an increase or decrease in plasma concentrations of saquinavir or of the coadministered drug. The manufacturer recommends caution when the following drugs are used concomitantly with saquinavir: calcium channel blockers, carbamazepine, clarithromycin, clindamycin, dapsone, dexamethasone, ketoconazole, phenobarbital, phenytoin, quinidine, rifabutin, and sildenafil.[39] [40]

Contraindications

Saquinavir and saquinavir mesylate are contraindicated in patients with clinically significant hypersensitivity to the drugs or any

components in the formulations. Caution should be used when administering saquinavir or saquinavir mesylate to patients with impaired hepatic function or hemophilia.[41]

Concomitant use of unboosted saquinavir or saquinavir mesylate with rifampin results in reduced plasma concentrations of saquinavir and is contraindicated.[42]

Recent data from a 28-day Phase I clinical trial of saquinavir/ritonavir 1000 mg/100 mg twice daily and rifampin 600 mg once daily showed significant hepatocellular toxicity in nearly 40% of patients. Transaminase elevations of up to 20 times the upper limit of normal were noted. Following drug discontinuation, clinical symptoms abated and liver function tests began returning to normal in all affected patients. Based on this data, the manufacturer recommends that rifampin should not be administered to patients taking ritonavir-boosted saquinavir as part of combination antiretroviral therapy.[43]

Clinical Trials

For information on clinical trials that involve Saquinavir, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Saquinavir AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[44]

Dosage Form: Saquinavir: Soft gelatin capsules containing saquinavir 200 mg; this formulation will be discontinued by February 15, 2006 because of decreased clinical demand.[45]

Saquinavir mesylate: Tablets containing saquinavir 500 mg; hard gelatin capsules containing saquinavir 200 mg.[46]

Saquinavir and saquinavir mesylate are not bioequivalent and cannot be used interchangeably. The recommended dose of saquinavir is 1,200 mg (taken as six 200 mg capsules) three times a day or 1,000 mg coadministered with 100 mg of ritonavir two times a day.[47] The recommended dose of saquinavir mesylate is 1,000 mg (taken as either

Saquinavir



Dosing Information (cont.)

two 500 mg tablets or five 200 mg capsules) coadministered with 100 mg of ritonavir twice a day. Both saquinavir and saquinavir mesylate should be taken within 2 hours after a full meal.[48]

Saquinavir mesylate is now the preferred formulation; the manufacturer encourages physicians to refrain from starting their patients on saquinavir soft gelatin capsule treatment and to discuss appropriate alternative treatment regimens for patients currently taking saquinavir soft gelatin capsules.[49]

Storage: Saquinavir: Store at 2 C to 8 C (36 F to 46 F) until dispensed. Patients can keep refrigerated capsules until expiration date. Once brought to room temperature (at or above 25 C [77 F]), capsules should be used within 3 months.[50]

Saquinavir mesylate: Store at 15 C to 30 C (59 F to 86 F) in a tightly closed bottle.[51]

Chemistry

CAS Name: Saquinavir: (S)-N-[(IS)-I-[(1R)-2-[(3S,4aS,8aS)-3-(tert-Butylcarbonyl)octahydro-2(1H)-isoquinoyl]-1-hydroxy-ethyl]phenethyl]-2-quinaldamidosuccinamide[52]

Saquinavir mesylate: (S)-N-[(alphaS)-alpha-[(1R)-2-[(3S,4aS,8aS)-3-(tert-Butylcarbonyl)octahydro-2(1H)-isoquinolyl]-1 hydroxyethyl]phenethyl)-2-quinaldamidosuccinamide monomethanesulfonate (salt)[53]

CAS Number: Saquinavir: 127779-20-8[54]

Saquinavir mesylate: 149845-06-7[55]

Molecular formula: Saquinavir: C₃₈-H₅₀-N₆-O₅ / Saquinavir mesylate: C₃₈-H₅₀-N₆-O₅.C-H₄-O₃-S[56]

Saquinavir: C68.04%, H7.51%, N12.53%, O11.92% / Saquinavir mesylate: C61.07%, H7.10%, N10.96%, O16.69%, S4.18% [Calculated][57]

Molecular weight: Saquinavir: 670.86 / Saquinavir mesylate: 766.96[58]

Physical Description: Saquinavir: White to off-white powder.[59] Saquinavir mesylate: White to off-white, very fine powder.[60]

Solubility: Saquinavir: Insoluble in water at 25 C.[61]

Saquinavir mesylate: Aqueous solubility of 2.22 mg/ml at 25 C.[62]

Other Names

Ro 31-8959/000 (Saquinavir)[63]

Ro 31-8959/003 (Saquinavir mesylate)[64]

Saquinavir monomethanesulfonate (Saquinavir mesylate)[65]

Saquinavir mesylate[66]

SQV[67]

Further Reading

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Saquinavir



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Manufacturer Information

Saquinavir
Roche Laboratories
340 Kingsland Street
Nutley, NJ 07110
(973) 235-5000

Invirase
Roche Laboratories
340 Kingsland Street
Nutley, NJ 07110
(973) 235-5000

Fortovase
Roche Laboratories
340 Kingsland Street
Nutley, NJ 07110
(973) 235-5000

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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Saquinavir



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Saquinavir



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Saquinavir



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